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[0001] The current invention concerns active substance preparing, an embedded with which or several active ingredients are into a protein matrix, whereby the proteins with transglutaminase are transversecrosslinked. The active substance preparing e.g. lie. as stable dry powders forwards. The invention relates to in addition food and feed contained such preparing, methods to the preparation of the dry powders and particular uses of the transversecrosslinked proteins. In the special one the invention concerns dry powders, the vitamins, food and feed additives, like e.g. Carotenoids contain. In addition various additives can be embedded.

[0002] Pulverulent vitamin and Carotinoid preparations are well known and become in the pharmaceutical industry as well as in the food and feed industry in large scale used. Like that many methods are described to the preparation of suitable preparations in the literature.

[0003] To the preparation of pulverulent preparing, in which oxidation-sensitive cloths like oil-soluble vitamins or carotenoids against oxidative influences protected to become to be supposed, become various manufacturing methods, in particular spraying method described.

[0004] In the German patent specification 1 035319 described becomes, as a dispersion of an oily vitamin becomes sprayed into an high excess of pulverulent starch with a small moisture content (bottom 8%). Water is extracted by the dry strong powder from the sprayed particles. Thereby they solidify, whereby a large amount of the starch remains sticking to the surface of the particles. In addition the excess strong portion must become separated and subsequent again the process supplied.

[0005] In the Swiss patent specification 488,455 stated becomes that used as propellant means a mixture becomes from inorganic substances, which consists of hydrophobic and water-absorbent substances. Thereby the danger of explosion, which exists by the dry, finely divided starch, is to become avoided.

[0006] From the Swiss patent specification 389,505 is known that the dispersion of the active ingredient becomes a cooled in, gaseous medium sprayed, in which the sprayed particles by cooling solidify. For this process heads of up to 15 m become required, in addition the temperatures must become significant bottom room temperature maintained.

[0007] An other method to the solidification of the sprayed particles can take place also via collection in a powder, which consists of metal salts of higher fatty acids. This method becomes 431,252 described in the Swiss patent specification.

[0008] An alternative method to the preparation of wirkstoffhaltigen, stable preparing becomes 0,618,001 described in the European patent specification. The here made preparation of the spherical particles, which represent an imbedding of the active ingredient in a mixture from various carriers, by forming globules from a primary oil in water emulsion, which does not consist of the addition from active ingredients, ölförmigen cloths, proteins and waters to the one with water mixable solvents first by controlled division, and separates the subsequent obtained globules. For the preparation of the globules a particular mixing system is required. The here obtained particles are given subsequent with an aldehyde, for example acetaldehyde, glutaraldehyde or glyoxal subsequent treatment, whereby a chemical crosslinking, which are expressed also in the water insolubility of the obtained material, and thus an additional stabilization of the active ingredient achieved become.

[0009] In the American patent specification 4,670,247 an other method becomes the preparation of crosslinked particles described. For this first an emulsion, those essentially from a oil-soluble vitamin, becomes a protective colloid like e.g. Gelatin and a reducing sugar exists, by a spraying and a drying process into pulverulent particles transfered. These particles become subsequent treated in a thermal process with temperatures between 105 and 180 DEG C. By a Maillard reaction between the amino group of the proteins and the Oxo groups of the reducing sugar a water insolubility becomes the drying powder particle achieved, which becomes achieved by a crosslinking of the matrix components.

[0010] In EP 782883 edible microcapsules described, which contain a capsule wall, become, which become prepared by salting the protein out with an edible salt and crosslinking of the capsule wall with transglutaminase.

[0011] If oxidation-sensitive compounds, into this cases in particular fat-soluble vitamins and carotenoids, come with air into contact, a made conversion with oxygen, which leads to an active substance loss by conversion to undesired compounds. In order to prevent this oxidation, one can add certain additions the preparing, which make these again fewer transmissive for oxygen by conversion with reactive groups of the proteins for the example and thus to the active ingredients a stabilizing protection lend. This can take place for example by means of the fact that becomes prevented by conversion of proteins with reducing sugars in the sense of a Maillard reaction the solubility of the proteins in waters. Further a crosslinking can become achieved by conversion of the proteins with aldehydes, which likewise lends support matrix an increased stability to that.

[0012] These methods show however certain disadvantages, which let it appear desirable to look for improved stabilization procedures. Thus the application of a Maillard reaction between a protein and reducing sugars means cases into each a thermal load and thus at least into small amounts a degradation of the active ingredient. In addition the products are inclined to a brownish coloring.

[0013] The use of aldehydes as crosslinking agents is linked with the serious drawback that here highly reactive and health most precarious additives become used. The products, which become prepared after these methods, find only conditional absolute acceptability with the consumer.

[0014] On the other hand the use of an enzymatic crosslinking means the avoidance of thermal processes and an addition of a cloth acceptable in each respect, who is a natural ingredient of each food chain as stabilizing principle both. In addition the products exhibit no brownish coloring.

[0015] The invention process to the preparation of active substance preparing covers the steps:

a) Mix aqueous solution from crosslinkable protein, transglutaminase and active ingredient

b) Spray,
whereby the weight ratio lies between active ingredient and protein between 1 to 10 and 4 to 1.

[0016] Prefered weight ratios between active ingredient and protein lie between 1 to 4 and 2 to 1, particularly prefered between 1 to 3 and 1 to 1.

[0017] Prefered crosslinkable proteins are gelatin, casein, Soja protein, corn protein and collagen.

[0018] Prefered ones are invention processes, sprayed with which a wirkstoffhaltige emulsion or dispersion becomes into an inert gas atmosphere loaded with hydrophobic silicic acid.

[0019] In addition methods are prefered, dried with those after the spraying become up to a residual moisture of bottom 10 Gew. - %, prefered bottom 6 Gew. - %.

[0020] The temperature of the invention process becomes essentially bottom 80 DEG C, prefered bottom 60 DEG C, maintained.

[0021] The invention relates to in addition active substance preparing available after an invention process, and such, which contain the 0,025-fachen to quadruple proportion by weight as additional feature concerning active ingredient at release agents or parting agent mixtures, as well as foods or feed contained such a active substance preparation.

[0022] Prefered release agents are hydrophobic silicic acid, corn starch, by chemical treatment hydrophobierte corn starch, metal salts of higher fatty acids and other vegetable starch.

[0023] In the case of hydrophobic silicic acid the portion lies concerning active ingredient prefered in a range between 0,025 and 0,4, particularly prefered between 0,05 and 0,2. With corn starch the corresponding ratio prefered lies between 0,25 and 2, particularly prefered between 0,5 and 1,5.

[0024] The active substance preparing according to invention are available essentially these active ingredients contained by preparation of a dispersion, a protein and an other carrier and bulking agents e.g. from the group of the carbohydrates and/or natural or chemical modified starch. It can contain still other additives such as stabilisers or emulsifying aids. In addition it contains an enzyme, which is in the layer to link on many way protein molecules with one another. The thereby achieved crosslinking lends to the protein and concomitantly that matrix, are embedded in which the active ingredients, a reduced water solubility and thus an increased stability.

[0025] The obtained active substance preparing are essentially homogeneous concerning the distribution of crosslinked matrixes.

[0026] Prefered crosslinkable proteins are gelatin, e.g. Bone gel, cattle gel, fish gel, milk proteins, like e.g. Casein, soy proteins, corn proteins and collagens, particularly prefered proteins are milk proteins and soy proteins. The crosslinking enzymes according to invention are transglutaminases, particularly such, which become from microorganisms recovered, in particular transglutaminases of microbial origin.

[0027] Prefered active ingredients are vitamins, food and feed additives. In particular hydrophobic active ingredients are prefered, particularly prefered such those light are more oxidizable. Such are the vitamins of the groups A, D, E and K. Prefered food and feed additives are carotenes and carotenoids such as beta - carotene and like e.g.: Astaxanthin, Astacin, Apo-8' more carotinsäureethylester, Citranaxanthin, Canthaxanthin, Zeaxanthin, Apo-8' carotinal, Lutein, Capsanthin, Lycopin and their mixtures.

[0028] The emulsion becomes using hydrophobic release agents like hydrophobic silicic acid, natural starch, like e.g. Corn starch, hydrophobierte starch derivatives, like e.g. hydrophobierte corn starch, salts of langkettigen fatty acids or mixtures from these cloths sprayed. In addition, the release agent can in the spray chamber e.g. as hydrophobic silicic acid particles in inert gas (e.g. Nitrogen) presented become. Subsequent one the made drying process of the sprayed particles if necessary after separation of the release agents, if necessary bottom light heating to 80 DEG C, prefered to 60 DEG C, particularly prefered with room temperature, by treatment in an air or an inert gas current.

▲ top

Example 1

[0029] In 360 g waters became 81.8 g gelatin (type A 100 Bloom) and 50.7 g Isosweet (company Amylum) dispersed and by 30-minütiges agitation with 60 DEG C in solution brought. Subsequent ones became 62.6 g corn starch in addition given, whereby other agitated became, until all components were uniform dispersed. Afterwards the made addition of 62,9 g vitamin A-acetate, which became stabilized by addition of Ethoxyquin (100 mg/millions I.E.) and BHT (4.5 mg/millions I.E.). The vitamin A was in-emulsified with the help of a high speed agitator into the aqueous phase. Finally the obtained emulsion became by addition of 10% iger aqueous sodium hydroxide solution to a pH value of 8,0 adjusted and with 20 ml an aqueous solution transglutaminase staggered bacterial of 200 of unit.

[0030] The obtained emulsion thereafter sprayed became with 55 DEG C over an a material nozzle with a pressure of 4,2 bar into a nitrogen atmosphere loaded with hydrophobic silicic acid. The obtained product became subsequent on a fluid bed dryer in the nitrogen stream with room temperature within 15 hr. on a residual moisture of 4,2% dried.

Example 2

[0031] In modification of the previous example a dry powder became, as described however prepared without addition of transglutaminase. This product white after drying a residual moisture content 3,9% up.

Example 3

[0032] A part of the dry powder from example 2 became prolonged tempered by thermal treatment in a rotary flask in an oil bath with 120 DEG C 20 min, whereby by Maillard reaction a brownish discoloration occurred. The residual moisture of the product sank with this process on content of 1,9%.

Example 4

[0033] A Astaxanthin formulation becomes prepared after methods described in EP 0,065,193 in the detail.

[0034] 30 g astaxanthin become mixed continuous from 30 bar with 370 g isopropanol in a mixing chamber in 240 g isopropanol common with 1,1 g Ascorbylpalmitat and 6.4 g Ethoxyquin suspended and with adjustment of the pressure relief valve. At a dosing speed of 6 l/h on the suspension side and of 9 l/h on the solvent side a mixture temperature of 173 DEG C becomes adjusted in the mixing chamber. After a residence time of 0,3 seconds the molecular-disperse solution in an other mixing chamber with one becomes on pH 9.5 adjusted solution of 38,6 g gelatin and 105 g dextrose in 4000 g waters with a throughput rate of 80 l/h mixed. One receives a colloid-disperse active substance suspension. The Teilchengrössenanalyse supplies an average value of 0,15 mu m with a distribution-wide of 31%.

[0035] At a thin section evaporator the Mikronisat up to a solid content of approx. becomes. 25% concentrated. Now with 60 DEG

C melted the concentrated product, 50 will become ml an aqueous solution of 250 of unit bacterial transglutaminase added and bottom-agitated with a sheet agitator in a four-neck piston.

[0036] The finished dispersion becomes into autoclaves a filled and with a nozzle into a container, which contains Sipernat D17 as spraying aid in air dispersed, sprayed. The so prepared dry powder is < on a fluid bed dryer with room temperature within 20 h on a moisture content of; 6% dried.

Example 5

[0037] From the obtained dry powders the fraction with the particle size 250 to 355 mu m out-sieved and a stability examination was submitted into a Standardprämix. For this became approx. 100 mg of the test patterns in Präparateglä weighed (for each pattern and test time 4 weighing), with 4 g Prämixmischung, existing from 60% wheat semolina bran, 30% 50% igem Cholinchlorid on silicic acid and 10% trace element mixture, existing from 37,43% CuSO4 x 5 H2O; 46.78% FeSO4 x 7 H2O; 11.79% ZnO; 3.61% MNO and 0.39% CoCO3 staggered and subsequent careful with the hand mixed.

[0038] The test patterns become in a climatic cabinet with constant temperature and humidity (40 DEG C and 70% rel. Moist) 6 weeks prolonged open stored. Starts of the storage, after 4 and 6 weeks the 4 becomes for the respective test time prepared test patterns removed and on the remaining remainder content of vitamin A active ingredient checked.

[0039] The test results are in the subsequent table shown:

Vitamin A-retention (%)

Attempt product

< tb> < TABLE> Columns=4
< tb>
< tb> Head Col 1: Dry powder
< tb> Head Col 2: Start (I.E. /g)
< tb> Head Col 3: after 4 weeks
< tb> Head Col 4: after 6 weeks
< tb> 1. with addition of Transglutaminase< SEP> 494.884< SEP> 86,7< SEP> 79,5
< tb> 2. without Transglutaminase< SEP> 520.924< SEP> 85,1< SEP> 76,6
< tb> 3. like 2., thermal behandelt< SEP> 526.144< SEP> 87,4< SEP> 80,7
< tb> < /TABLE>

Example 6

[0041] In accordance with example 1 water, 102.3 g gelatin 100 Bloom A, became 63.4 g Isosweet, 76.5 g vitamin A-acetate with 420 g (2.16 millions I.E. /g; stabilized with 100 mg Ethoxyquin/million I.E. and 14.5 mg BHT/Mio I.E.) and 80.6 g corn starch an emulsion prepared, which became subsequent sodium hydroxide solution aqueous with 10% iger to a pH value of 8,0 adjusted. This emulsion became treated in three same portions divided and as follows:

A: no addition
B: Addition of 2,05 g of a one percent preparation of transglutaminase (*TG*) in a polysaccharide
C: Addition of 5,11 g of a one percent preparation of transglutaminase (*TG*) in a polysaccharide

[0042] The emulsion became in accordance with example 1 into a nitrogen atmosphere sprayed loaded with hydrophobic silicic acid.

[0043] Approach A became in the nitrogen stream with room temperature on a residual moisture of 3,1% dried. Of it a part became additional with 120 DEG C 20 min tempered.

[0044] Approach B became both with room temperature dried and after a storage of 15 hr. with room temperature likewise in the fluidized bed dried.

[0045] Approach C became corresponding approach B treated.

[0046] The obtained products were submitted in accordance with example 5 of a stability examination. The determined data become assembled in appended table.
< tb> < TABLE> Columns=6
< tb>
< tb> Head Col 1: Product
< tb> Head Col 2: Treatment
< tb> Head Col 3: Vitamin A content (I.E. - /g)
< tb> Head Col 4: Remainder-moist (%)
< tb> Head Col 5: Retention after 4 weeks (%)
< tb> Head Col 6: Retention after 6 weeks (%)
< tb> < SEP> Without Zusatz< SEP> Fluid bed Tr. (= drying process) < SEP> 548.700< SEP> 3,1< SEP> 53,9< SEP> 29,1
< tb> < SEP> Without Zusatz< SEP> Fluid bed Tr. + therm. Vernetzung< SEP> 563.300< SEP> 1,5< SEP> 63,8< SEP> 45,9
< tb> < SEP> 2.05 g TG< SEP> Fluid bed Tr.< SEP> 543.600< SEP> 3,9< SEP> 56,2< SEP> 34,5
< tb> < SEP> 2.05 g TG< SEP> 15 hr. Blank + fluid bed Tr.< SEP> 541.900< SEP> 3,4< SEP> 54,8< SEP> 32,4
< tb> < SEP> 5.11 g TG< SEP> Fluid bed Tr.< SEP> 540.000< SEP> 3,2< SEP> 62,6< SEP> 35,5
< tb> < SEP> 5.11 g TG< SEP> 15 hr. Blank + fluid bed Tr.< SEP> 544.600< SEP> 3,6< SEP> 64,4< SEP> 39,7
< tb> < /TABLE>
< tb> < TABLE> Columns=4
< tb>
< tb> Head Col 1: Product
< tb> Head Col 2: Treatment
< tb> Head Col 3: Diffusion rate (usec, rope)
< tb> Head Col 4: Intensity (kcps)
< tb> < SEP> Without Zusatz< SEP> Fluid bed Tr.< SEP> 596,3< SEP> 559,3
< tb> < SEP> 581,2< SEP> 579,0
< tb> < SEP> 552,2< SEP> 543,3
< tb> < SEP> Without Zusatz< SEP> Fluid bed Tr. + therm. Crosslinking
< tb> < SEP> 2.05 g TG< SEP> Fluid bed Tr.< SEP> 510,7< SEP> 545,4
< tb> < SEP> 514,6< SEP> 536,4

< tb> < SEP> 496,9< SEP> 536,4
< tb> < SEP> 2,05 TG< SEP> 15 hr. Blank + fluid bed Tr.
< tb> < SEP> 5,11 g TG< SEP> Fluid bed Tr.< SEP> 544,0< SEP> 518,3
< tb> < SEP> 574,4< SEP> 539,1
< tb> < SEP> 549,5< SEP> 542,3
< tb> < SEP> 5,11 g TG< SEP> 15 hr. Blank + fluid bed Tr.
< tb> < /TABLE>

[0047] Gelatin is a mixture of various large protein molecules. All molecules become labeled by the fluorescent dye. With strong crosslinking only the smallest molecules in the observation period succeed in leaving the network of the transversecrosslinked gelatin. Beyond that smaller molecules have a smaller probability to be by a crosslinking direct affected. Observed one one by FK the molecular size in the projection of the transversecrosslinked gelatin strong by transglutaminase, then one finds an high diffusion rate (rope in mu seconds is smaller as in the control) - to typical for small molecular sizes. Also it is to be observed that the intensity (I, kcps) is to a large extent more comparable between all samples.

Example 7

[0048] In an other trial a Astaxanthin dispersion became bottom addition of varying amounts transglutaminase in accordance with example 4 dry powders processed.
< tb> < TABLE> Columns=4
< tb>
< tb> Head Col 1: Addition
< tb> Head Col 2: Treatment
< tb> Head Col 3: Active substance content t (%)
< tb> Head Col 4: Retention after 6 weeks (%)
< tb> < SEP> Ohne< SEP> With blank getrocknet< SEP> 11,4< SEP> 67
< tb> < SEP> 0.01% TG< SEP> With blank getrocknet< SEP> 11,5< SEP> 80
< tb> < SEP> 0.05% TG< SEP> With blank getrocknet< SEP> 11,2< SEP> 75

Blank = room temperature SIMILAR 23 DEG C
< tb> < /TABLE>